Addition of gemcitabine to paclitaxel, epirubicin, and cyclophosphamide adjuvant chemotherapy for women with early-stage breast cancer (tAnGo)

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Gemcitabine added to paclitaxel-containing, epirubicin / cyclophosphamide-based, adjuvant chemotherapy for women with early stage breast cancer (*tAnGo*): an open-label, randomised, phase 3 trial

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Short title: *tAnGo*: An adjuvant breast cancer trial of sequential EC-GT

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ABSTRACT

Background: *tAnGo,* an international phase III trial, was designed to evaluate the potential role of gemcitabine when added to anthracycline and taxane-containing adjuvant chemotherapy for early breast cancer (EBC). At the time the study was developed gemcitabine had shown significant activity in metastatic breast cancer, and there was evidence of a favourable interaction with paclitaxel.

Methods: *tAnGo* entered women of 18 years or older, with newly diagnosed, early stage breast cancer who had a definite indication for chemotherapy, any nodal status, any hormone receptor status, and adequate marrow, hepatic and renal function. *tAnGo* was a randomised phase 3, open-label, superiority trial. The primary endpoint was disease-free survival (DFS) and the trial aimed to detect 5% differences in 5-year DFS rates between EC-GT (4 cycles of epirubicin 90mg/m^2 IV (E) and cyclophosphamide 600mg/m^2 IV (C) day1 every (q) 3 weeks, followed by 4 cycles of paclitaxel 175mg/m^2 /3hour infusion (T) day1 with gemcitabine 1250mg/m^2 IV (G) days1 and 8, q3 weeks) and EC-T. Overall survival (OS) was a secondary endpoint. Patients were randomised by a central computerised deterministic minimisation procedure, with stratification by country, age, radiotherapy intent, nodal status, oestrogen (ER) and HER2 receptor status. Recruitment completed in 2004 and this is the final, intention-to-treat analysis. This trial is registered with EudraCT (2004-002927-41), ISRCTN (51146252), and ClinicalTrials.gov (NCT00039546).

Results: Between August 2001 and November 2004, 3152 patients were randomised from the UK and Ireland, by 127 centres; 1576 to EC-GT, and 1576 to EC-T. Patient characteristics were balanced across treatment groups: 77% node positive, 55% $\leq$50 years old, 62% of tumours grade 3, 63% >2cm, 44% ER negative, 50% PgR negative, 13% HER2 positive. This protocol-specified final analysis has a

median follow-up of 10 years (IQR 10-10 years) and recorded 1087 DFS events and 914 deaths. No statistically significant difference between treatments was observed in DFS (adjusted HR=0·97 (95%CI 0·86-1·10) p=0·64) or OS (adjusted HR=1·02 (95%CI 0·89-1·16) p=0·81). No benefit for EC-GT was found in any of the protocol-determined subgroups. Toxicity, dose intensity and a detailed safety sub-study showed both regimens to be safe, deliverable and tolerable. Grade 3 and 4 toxicities were reported at expected levels in both groups. Most commonly suffered (in 1565 EC-GT pts vs 1567 EC-T pts respectively) were neutropenia (Grade 3: 323 (21%) vs 212 (14%); Grade 4: 204 (13%) vs 200 (13%)): muscle and joint pains (Grade 3: 200 (13%) vs 175 (11%); Grade 4: 7 (<1%) vs 11 (1%)): fatigue (Grade 3: 198 (13%) vs 140 (9%); Grade 4: 9 (1%) vs 12 (1%)): infection (Grade 3: 194 (12%) vs 131 (8%); Grade 4: 8 (1%) vs 10 (1%)): vomiting (Grade 3: 134 (9%) vs 101 (6%); Grade 4: 9 (1%) vs 7 (1%)): nausea (Grade 3: 132 (8%) vs 102 (7%)).

Interpretation: The addition of gemcitabine to anthracycline and taxane-based adjuvant chemotherapy at this dose and schedule confers no therapeutic advantage in terms of DFS and OS in early breast cancer although it did cause more toxicity. Therefore gemcitabine has not been added to standard adjuvant chemotherapy in breast cancer for any subgroup.

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Key Words: *tAnGo*, early breast cancer, adjuvant chemotherapy, EC-T, gemcitabine.

INTRODUCTION

Despite the therapeutic advances of the last three decades, the development of more effective adjuvant therapy remains a priority for improving the treatment of women with early breast cancer The modest impact of traditional adjuvant polychemotherapy (mainly cyclophosphamide, methotrexate, 5-fluoruracil [CMF]) had been confirmed as a 24% global reduction in the risk of relapse or death (hazard ratio (HR)=0·76) and a 15% reduction in the risk of death (HR=0·85) in the meta-analysis by the Early Breast Cancer Trialists Collaborative Group[1]. The incorporation of anthracyclines provided additional benefits, with an estimated HR for relapse or death of 0·88 compared with CMF[1], and a HR $\leq$ 0·7 in individual trials with higher dose epirubicin-based adjuvant regimens[2-4]. Following the routine inclusion of anthracyclines into standard adjuvant treatment, both the CALGB 9344[5] and NSABP B28[6] trials showed that the sequential addition of four cycles of paclitaxel to standard therapy with four cycles of doxorubicin and cyclophosphamide further reduced the risk of recurrence. CALGB 9344 reported that the risk of relapse or death was reduced by 17% (HR=0·83 (95%CI 0·73-0·94), p=0·0013) and the risk of death by 18% (HR=0·82, (0·71-0·95), p=0·0061)[5] The NSABP B28 trial confirmed a HR=0·83 (0·73-0·95), p=0·008) for relapse or death and a non-significant improvement in overall survival. A meta-analysis of polychemotherapy conducted by the EBCTCG confirmed the benefits of the addition of taxanes to anthracycline-based polychemotherapy regimens[7].

Based on pre-clinical evidence of a potentially favourable interaction between paclitaxel and gemcitabine, and the favourable results of a pivotal randomised phase III trial comparing paclitaxel and gemcitabine in combination against single agent

paclitaxel in patients who had anthracycline pre-treated metastatic disease, it seemed plausible that the addition of gemcitabine to paclitaxel in the anthracycline / cyclophosphamide (AC-T) regimen might further improve DFS and OS in early stage disease. The *tAnGo* trial was designed to evaluate the addition of gemcitabine to a sequential epirubicin and cyclophosphamide followed by paclitaxel regimen. The only other adjuvant trial in breast cancer testing the addition of gemcitabine to standard chemotherapy was NSABP-B38[8], a three arm trial with gemcitabine added to doxorubicin /cyclophosphamide and paclitaxel (AC-TG).

The *tAnGo* trial was one of the first breast cancer trials to have a 'companion' neoadjuvant study (Neo-*tAnGo*) which reported in 2014[9]. Both the endpoint of pathological complete response (pCR) from the Neo-*tAnGo* trial, which directly tests the chemo-sensitivity of the combination on the primary tumour, and the long term outcomes of DFS and OS from the *tAnGo* trial reported in this manuscript, are now available.

A preliminary safety analysis without outcome data on the first 135 patients reported in 2008, demonstrated that both regimens were well tolerated, with only temporary changes in pulmonary function and transaminitis[10]. The preliminary results of *tAnGo* were presented as a conference abstract in 2008 at a median of 3 years follow-up[11], and showed no benefit from the addition of gemcitabine (DFS HR=1·0 (95%CI 0·8-1·2), p=0·96, OS HR=1·1 (95%CI 0·9-1·4), p=0·35). The present manuscript provides the only definitive and final analysis of the trial. All *tAnGo* patients were randomised more than 10 years ago, and we report here the long-term results for

DFS and OS at a median follow-up of 10 years (IQR 10-10 years) alongside the 5- and 10-year detailed safety study findings.

METHODS

Study design and participants

The *tAnGo* phase III randomised trial was designed to test the hypothesis that the addition of gemcitabine to the second phase of a standard regimen of epirubicin and cyclophosphamide followed by paclitaxel (EC-GT) improves disease-free survival (DFS) in comparison to epirubicin and cyclophosphamide followed by paclitaxel alone (EC-T) in women with early stage breast cancer with a definite indication for adjuvant chemotherapy.

We enrolled women aged 18 years or older with completely excised invasive early breast cancer of any nodal or hormone receptor status. Patients were enrolled where according to risk, a definite indication for adjuvant chemotherapy existed. This included ER negative (defined as Allred score 0-2); ER weakly positive (Allred score 3-5); and grade 3 tumours, and in these categories recruitment was regardless of nodal status. Patients with ER strongly positive (Allred Score 6-8) or grade I or II tumours were usually included only if positive axillary lymph nodes were present. Other eligibility criteria included adequate bone marrow, hepatic, and renal function, adequate (0-1) ECOG performance status, no previous exposure to chemotherapy or radiotherapy, no previous or concomitant cancer, the ability to commence chemotherapy within 8 weeks of surgery, and written informed consent. Women were enrolled at 127 sites in the UK and 2 in Ireland.

At the start of the trial, eligibility criteria stated that tumours must be either ER-negative (defined as Allred score 0-2) or weakly positive (Allred score 3-5) and, in the case of weakly ER-positive breast cancer, these must be either PgR-negative or weakly positive (Allred score 3-5). In 2003, after 550 patients had been recruited, the protocol was amended and these initial criteria were relaxed to include patients with any hormone receptor status, given the evidence that was accruing during the trial recruitment phase, for taxane activity irrespective of hormone receptor status. Full eligibility can be found in the trial protocol.

After completion of trial therapy, the guidance was that all ER-positive patients should receive 5 years of adjuvant treatment (tamoxifen or an aromatase inhibitor) either within another trial or as standard treatment. The protocol anticipated both clinical trials of other hormonal therapy and tamoxifen duration beyond 5 years. Patients had follow-up usually carried out by oncologists and this was advised at appropriate intervals for the higher risk patients included in the trial. These follow-up intervals allowed accurate and timely capture of relapse events, as well as allowing proper documentation of toxicity and its resolution. After completion of trial treatment follow-up intervals were 3-monthly for 6 months, then 6-monthly for 3 years, and then annually to ten years after diagnosis.

The *tAnGo* trial was an investigator designed and led trial, approved by the MHRA on 06-Sep-2000, the West Midlands Multi-Centre Research Ethics Committee on 11-Dec-2000 and by all Local Research Ethics Committees and Research and Development Departments at participating hospitals. The trial was centrally coordinated by the Cancer Research UK Clinical Trials Unit, University of

Birmingham with regional coordination being provided by the Clinical Trials Research Unit, University of Leeds, the ISD Cancer Clinical Trials Team, Partner in CaCTUS in Edinburgh and Cancer Trials Ireland (formerly the All Ireland Cooperative Oncology Research Group - ICORG), Dublin, Ireland. Statistical support was provided by Warwick Clinical Trials Unit, University of Warwick.

Randomisation and masking

The open-label *tAnGo* trial used a central computerised deterministic minimisation procedure to randomise patients (1:1) between EC-GT and EC-T treatment regimens (Figure 1). Treatment allocation was made by telephone to one of the three regional trials offices (Birmingham, Leeds or Edinburgh). Stratification was by country (England, Scotland, Wales, Republic of Ireland, Northern Ireland), age (<=50, >50 years old), radiotherapy intent (planned, not planned), nodal status (negative, 1-3 nodes positive, 4+ nodes positive), ER status (negative, weakly positive, strongly positive) and HER2 status (3+, other [0, 1+, 2+], unknown).

Procedures

The primary endpoint was disease-free survival and secondary endpoints were overall survival, toxicity, delivered dose-intensity, tolerability and serious adverse events and were all investigator assessed and reported to the University of Birmingham CRCTU. For all patients adverse events were recorded for each chemotherapy cycle according to Common Terminology Criteria for Adverse Events (CTCAE) v2·0 grade.

Control arm chemotherapy was epirubicin 90mg/m^2 IV with cyclophosphamide 600mg/m^2 IV day1 every (q) 3 weeks for 4 cycles, followed by paclitaxel 175mg/m^2/3hour infusion day1 q 3 weeks for 4 cycles (EC-T). Investigational arm chemotherapy was the same with the addition of gemcitabine 1250mg/m^2 IV days1 and 8 q3 weeks to the paclitaxel (EC-GT).

If neutropenic fever or sepsis occurred after a cycle of chemotherapy, the next cycle was delayed until the absolute neutrophil count was at least $1{\cdot}0 \times 10^9$ cells per L. Following a delay, either dose reduction of all drugs to 80%, or GCSF support with 100% dose were allowed, and all remaining cycles of the same four-cycle block were given at those doses. For persistent thrombocytopenia, the next cycle was delayed until patients had at least 100×10^9 platelets per L and was reduced to 80%, maintaining this dose reduction for subsequent cycles. Primary prophylaxis with GCSF was not provided with either epirubicin and cyclophosphamide or paclitaxel (with or without gemcitabine). Once started, prophylactic GCSF was usually continued into the second phase of chemotherapy at the discretion of the responsible physician. Day 8 FBC values had no impact on treatment decisions.

If grade 2 neuropathy occurred during treatment with paclitaxel, remaining doses were reduced to 135 mg/m² (gemcitabine was unchanged). If grade 3 neuropathy occurred, either gemcitabine continued alone or trial chemotherapy was discontinued.

Gemcitabine was dose-reduced to 80% in the event of grade 3 hepatic toxicity (transaminitis; aspartate aminotransferase or alanine aminotransferase ≥5–20 ×

upper limit of normal [ULN]) on day of treatment at clinician's discretion, because transaminitis is not known to affect gemcitabine clearance. We were unable to substantiate earlier concerns about gemcitabine's potential for clinically significant hepatic impairment. In the event of gemcitabine-related pulmonary toxicity of CTCAE grade 2 or worse, the patient was discontinued from study therapy.

Cardiac toxicity was not anticipated at the cumulative epirubicin dose of 360 mg/m^2 but if congestive cardiac failure developed, patients were investigated and treated as appropriate, epirubicin was discontinued, and other chemotherapy was given at the discretion of the treating clinician.

For allergic reactions to paclitaxel, the infusion was stopped if mild symptoms of skin rash, flushing, and localised pruritus occurred (Grade 1 and 2). Intravenous steroids and antihistamines were given and immediate slow re-challenge of chemotherapy was used on recovery. Paclitaxel infusion was stopped if moderate symptoms of generalised pruritus or rash, mild dyspnoea, or mild hypotension occurred and intravenous steroids and antihistamines were given (Grade 3). 48 h of steroids were then advised before cautious paclitaxel re-challenge. If severe symptoms occurred, including bronchospasm, generalised urticaria, angio-oedema, hypotension (systolic blood pressure <100 mm Hg), or life-threatening anaphylaxis (Grade 4), paclitaxel infusion was stopped and treatment was given with intravenous steroids, and intravenous antihistamines and if necessary intramuscular epinephrine 1 mL 1:1000; re-challenge was not recommended.

Radiotherapy was given according to local protocols, with radiotherapy intent employed as a stratification factor (planned at randomisation, not planned at randomisation). Any endocrine treatment was to be stopped prior to commencing chemotherapy, and recommenced as appropriate afterwards according to local protocols. The *tAnGo* trial was completed before adjuvant trastuzumab was used routinely and therefore the protocol did not include guidelines for adjuvant trastuzumab in HER2 positive patients. Patients could be recruited into the HERA Trial[12]. Clinical surveillance was continued for 10 years at the clinical centres.

To investigate standard prognostic markers and treatment interactions, routine pathology tissue blocks from surgery were retrieved for 2462 of the 3141 eligible patients (78%) and were reviewed centrally in Cambridge (EP) for breast cancer morphology, tumour grade, histotype and scoring of ER, PR and HER2 on immunohistochemistry (IHC). Tissue microarrays (TMAs) were constructed with a single 0·6mm core from a representative part of the tumour (172 sample arrayed in each TMA block) and sections stained for ER, PR and HER2 by IHC, with additional FISH for those in the HER2, 2+ category. When central testing was not available (22%), results from the local report were included for the biomarker analysis.

Outcomes

The primary outcome measure of DFS was calculated from date of randomisation to date of first relapse (loco-regional or distant, not including DCIS); to date of death in women dying without relapse; or to date of censor in women alive and relapse-free. The secondary outcome of overall survival was calculated from date of randomisation to date of death, or date of censor if alive.

Cardiac, pulmonary and hepatic function were initially monitored at four time points (randomisation, mid-chemotherapy, post-chemotherapy and 6-months post-chemotherapy) and showed the treatment regimens as equally well tolerated, only causing mild to moderate reduction in pulmonary function, which recovered completely by 6 months, and gemcitabine causing increased levels of liver transaminases but no adverse clinical events[10]. For the evaluation of long-term toxicity, these assessments were also undertaken at 5 and 10 years post-treatment.

Statistical Analysis

The original sample size calculations for *tAnGo* assumed a 5-year DFS of 45-55% from patients randomised onto the control arm of the trial, given that all patients were to be ER negative. Using this, 3000 patients were deemed necessary to detect (with 5% two-sided significance,) differences in survival rates in excess of 5% with 80% power. This would also allow detection of differences in excess of 7% with 85% power and in excess of 10% with 99% power.

When the eligibility criteria for *tAnGo* were changed in September 2003, to include lower risk patients who were ER positive and PgR either positive or unknown, 550 patients had already been randomized. The effect on the expected 5-year DFS of the control arm of the trial was assessed, along with the most up-to-date 5-year DFS estimates for early stage breast cancer based on the recent CALGB 9344 and NEAT results. Following discussions with the trial Data and Safety Monitoring Committee (DSMC), it was determined that the 5-year DFS estimate for control arm patients was approximately 70% and that the power of the study to detect in excess of 5%

differences with 5% two-sided significance had in fact increased from 80% to 85%. *tAnGo* thus continued to aim for the 3000 patient target.

Survival curves were constructed using Kaplan-Meier methodology. Log-rank tests assessed differences in patient and tumour characteristics, and treatment. Cox-proportional hazards modelling investigated and adjusted for prognostic factors. Hazard ratios of treatment effects on the risk of relapse and death were calculated for prognostic subgroups and displayed as forest plots. Secondary outcome measures were adverse effects and dose intensity. An additional log-rank analysis was undertaken censoring non-breast-cancer deaths at date of death, to assess the sensitivity of the DFS and OS results.

The maximum Common Toxicity Criteria (CTC) grades for a list of common toxicities reported for all patients during their chemotherapy was examined.

The methods for dose intensity calculations have previously been described[13]. We compared course delivered dose intensities (CDDI) across treatment groups with Wilcoxon rank sum tests and chi-squared tests with continuity corrections.

Using Pocock's method of assigning equal weighting to the alpha spend, with significance determined by p=0·022[14], three event driven, primary endpoint analyses were planned: the first at 18 months minimum follow-up (min FU, 280 events expected) allowing detection of differences in excess of 10% with 95% power; the second at 30 months min FU (550 events expected) allowing detection of differences in excess of 7% with 95% power; the third at 60 months min FU (920 events

expected) allowing detection of differences in excess of 5% with 90% power. The protocol did not set out rules for stopping the trial early due to futility during the recruitment phase. However, through the course of the trial, the TMG and DSMC defined and agreed on the plans for stopping rules for futility. These included the pre-defined acceptable limit of the conditional power analyses to be undertaken at the interim analyses time-points.

In June 2006, the *tAnGo* DSMC scrutinised the first pre-planned primary endpoint analysis and considered it too early to release the results. In November 2007, the second pre-planned analysis showed the conditional power[15] was 7%, below the 10-15% level pre-set by the DSMC thus making it very likely that the final results would be consistent with the current results. The DSMC therefore recommended the trial data be released and they were presented at ASCO 2008[11]. Results of the third and final pre-planned primary endpoint analysis (minimum 60 months FU, 920 events expected) are presented here.

Statistical analysis was undertaken by Warwick Clinical Trials Unit, using SAS statistical software (version 9·4). All reported p-values are two-sided. All patients who were protocol violators were analysed within their randomised groups thus allowing analysis to be undertaken on an intention-to-treat basis. *tAnGo* is registered with ISRCTN (51146252), EudraCT (2004-002927-41), and ClinicalTrials.gov (NCT00039546).

Role of the funding source

The trial was endorsed by Cancer Research UK and supported by CRUK Clinical Trials Unit at University of Birmingham core infrastructure and a grant from Breast Cancer Relief. In addition unrestricted educational grants were provided by Eli Lilly and Company Limited, Pfizer Limited and Bristol-Myers Squibb Pharmaceuticals Limited. Gemcitabine (Gemzar^{TM}) and Paclitaxel (Taxol^{TM}) were provided free of charge by Eli Lilly and Company Limited and Bristol-Myers Squibb Pharmaceuticals Limited respectively. Neither the sponsors of the study nor the pharmaceutical companies had any role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors (HE and LH) had full access to all of the data and (with CJP) had final responsibility for the decision to submit for publication.

RESULTS

Patients

tAnGo recruited 3152 patients from 175 clinicians at 127 centres in the UK and Ireland between 22nd August 2001 and 26th November 2004. Eleven patients (0·3%) were ineligible for the trial (6 EC-GT, 5 EC-T), principally for pre-existing metastases found after randomisation, leaving 3141 eligible patients for analysis (Figure 1). The discovery of the 11 patients' ineligibility for the trial was independent of the individual patient's randomisation allocation. Patient characteristics, type of operation, timing of surgery (Table 1) and tumour characteristics (p.1 Appendix) for the 3141 eligible patients (1570 EC-GT, 1571 EC-T) appear balanced between the two treatment groups.

Treatment Compliance

Protocol violations in treatment allocation were noted by the trial management committee in 19 patients (0·6% of 3141, 7 (0·4%) EC-GT, 12 (0·8%) EC-T) (Figure 1). All analyses included these patients in their original randomised treatment group, according to the intention-to-treat principle.

Use of other first-line treatments

Of the 287 pts known to be HER2 positive, 118 (41%) were reported, at some point on their FU forms, to have received trastuzumab (54 EC-GT pts (40% of 135), 64 EC-T pts (42% of 152)), of which 60/287 (21%) received trastuzumab as adjuvant treatment and 58/287 (20%) for relapsed disease. At baseline, radiotherapy was planned to be administered in 90% of patients (2823/3141; 90% (1412/1570) of EC-GT patients, 90% (1141/1571) of EC-T patients). Radiotherapy administration is unknown in 15 patients. In the remaining 3126 patients, 2754 (88%) are recorded as having received radiotherapy treatment. Rates are equal across treatment arms (1378 (88%) EC-GT patients and 1376 (88%) EC-T patients receiving radiotherapy, p=0·99). In terms of adjuvant hormonal treatment for ER-positive patients, the follow up data indicates that the guidance detailed in Methods was followed, and the majority received 5 years of tamoxifen.

Disease-Free and Overall Survival

At the data lock on 29th September 2016, 914 patients had died (29% of the 3141 eligible patients; 459/1570 (29%) EC-GT patients; 455/1571 (29%) EC-T patients: Figure 1). Breast cancer was listed most frequently as the main cause of death (792/914 (87%), p. 2 Appendix), but for the 122 patients for whom breast cancer was not listed as the main cause of death, 40/122 (33%) had already had a breast cancer

relapse. Therefore 82 patients (9% of 914) died without evidence of recurrent breast cancer. The median follow-up for the 2227 pts recorded as being alive was 10 years (IQR 10-10 years), with 96% having more than 8 years follow-up. Loco-regional and/or distant relapse was recorded in 995 (32%) women (31% EC-GT, 32% EC-T), with distant metastases being predominantly in the bone, liver and/or lung. There were 1087 events (35% of 3141 patients; 538/1570 (34%) EC-GT; 549/1571 (35%) EC-T) in the analysis of DFS. 213 patients (7% of 3141; 109/1570 (7%) EC-GT; 104/1571 (7%) EC-T) had second primaries recorded.

There was no significant difference between treatment groups in terms of DFS (log-rank p=0·63, adjusted hazard ratio (HR) 0·97 (95%CI 0·86-1·10), adjusted p=0·64, Figure 2a). DFS rates at 2, 5 and 10-years were similar for EC-GT and EC-T patients (2-year 88% vs 87%; 5-year 75% vs 74%; 10-year 65% vs 65% respectively). There were also no significant differences between treatment groups observed in OS (log-rank p=0·85, adjusted HR 1·02 (95%CI 0·89-1·16), adjusted p=0·81, Figure 2b). OS rates at 2, 5 and 10-years were similar for EC-GT and EC-T patients (2-year 93% vs 94%; 5-year 82% vs 82%; 10-year 70% vs 71% respectively). A sensitivity analysis of breast cancer-specific survival across treatment groups, analysing the 792 deaths due to breast cancer showed similar results (389 EC-GT, 403 EC-T), log-rank p=0·66, adjusted HR 0·97 (95%CI 0·85-1·12), adjusted p=0·71).

Univariate analysis showed that the following were significantly associated with worse DFS: higher nodal burden, negative ER/PR status, radiotherapy planning, larger tumour size, higher tumour grade, the presence of vascular/lymphatic invasion, mastectomy (all p<0·0001), poorer ECOG performance status (p=0·004),

positive HER2 status (p=0·0026), and triple negative phenotype (p=0·01) (Table 2). Similar results were found for OS (p.3 Appendix).

Plots of hazards over time for DFS and OS highlighted the similarity of the two randomised treatment arms (p.4 and 5 Appendix). However, in an exploratory analysis, for the HER2 negative patients, we demonstrated the expected significant differences between the ER negative sub-group (TNBC) and the ER positive subgroup in hazards over time; TNBC patients showed increased hazards for relapse and death in the early years, with a plateau of risk between 5 and 10 years, whilst ER positive patients showed persisting, albeit lower risks, for relapse and death at 10 years. In the smaller HER2 positive group ER negative and ER positive sub-groups showed a similar pattern of changes with increased risk of relapse in the early years for both, although higher hazards for ER negative patients. Of note, only 21% of HER2 positive patients received adjuvant trastuzumab.

Interaction of Treatment Effect with Prognostic Factors

Forest plots confirmed the lack of treatment effect on DFS in all subgroups of patients, specifically by age, ER, PR, nodal and HER2 status, performance status, surgery, tumour size, grade, and presence or absence of vascular or lymphatic invasion, triple negative status and ER/PGR negative status (Figure 3a-3c). Additionally no significant interactions with treatment effect were noted for these variables. Similar results were obtained for overall survival (p.6-8 Appendix). A non-pre-planned analysis was also carried out by four subgroups defined in the Neo-*tAnGo* manuscript[9] using Grade 3 patients only and splitting by ER combined with HER2 status. These four subgroups showed significant heterogeneity in DFS

(p=0·02) and borderline heterogeneity in OS (p=0·06), with a numerical trend for benefit from gemcitabine in the ER-/HER2+/G3 and ER-/HER2-/G3 subgroups (Figure 3c and p.8 Appendix).

Adverse Effects of Chemotherapy

Information regarding adverse effects was available from 3132 patients with full sets of treatment forms returned (99·7% of the 3141 eligible patients). Frequencies of patients reporting grades 3 and 4 toxicities are as expected (Table 3). Grade 3 (G3) toxicities were reported more commonly with EC-GT (1565pts) than EC-T (1567pts) for neutropenia (323 (21%); 212 (14%)): muscle and joint pains (200 (13%); 175 (11%)): fatigue (200 (13%); 140 (9%): infection (194 (12%); 131 (8%)): vomiting (134 (9%); 101 (6%)): nausea (132 (8%); 102 (7%)): neuropathy (83 (5%); 66 (4%)): fever (69 (4%); 46 (3%)): diarrhoea (43 (3%); 29 (2%)): constipation (41 (3%); 24 (2%)): anaemia (27 (2%); 11 (1%)): deep venous thrombosis (17 (1%); 9 (1%)): and thrombocytopenia (14 (1%; 7 (<1%)). G3 toxicities were similar in both arms (3132 pts) for dyspnoea (67 (2%)); stomatitis (56 (2%)): rash (46 (1%)); as was the only significant G4 toxicity, neutropenia (404 (13%)). 83/1565 (5%) of EC-GT patients discontinued chemotherapy for drug related toxicity and 45/1567 (3%) EC-T patients.

In total, 1158 serious adverse events (SAEs) were reported (650 during EC, 136 during T and 372 during GT cycles), involving 816 (26% of 3141) patients (474 (30% of 1570) EC-GT patients, 342 (22% of 1571) EC-T patients). 1121 (97%) of these were evaluated as serious adverse reactions (SARs), involving 794 (25% of 3141) patients. There were 31 suspected unexpected serious adverse reactions (SUSARs) recorded (20 by EC-GT patients, 11 by EC-T patients).

Detailed Safety Sub-study – Long-term toxicity assessments

There were 135 patients (69 EC-GT, 66 EC-T) included in the detailed safety sub-study. The assessment completion rate at 5-years post treatment was 75% (73 of the 97 patients alive; 72% EC-GT (34 of the 47 alive) and 78% EC-T (39 of the 50 alive)). At 10-years, assessment completion rates were 74% (63 of the 85 patients alive; 78% EC-GT (31 of the 40 alive) and 71% EC-T (32 of the 45 alive)). In total, 49 patients completed all 6 assessments (58% of the 85 alive at 10-years; 25 (63%) EC-GT, 24 (53%) EC-T). There were no long-term safety signals of significant concern (p.9 Appendix).

Early Deaths

19 patients (0·6% of the 3141 eligible patients) died within 3 months of completing their last chemotherapy cycle (10 (0·6% of 1570) EC-GT, 9 (0·6% of 1571) EC-T). 14 of these patients (7 EC-GT, 7 EC-T) died with metastatic breast cancer more than 30 days after day 1 of their last chemotherapy cycle and this indicates that they were likely to have had metastatic disease at the time of randomisation. In addition, one EC-T patient died of a second primary lung cancer and one EC-GT patient by suicide. Chemotherapy possibly contributed to 3 deaths: one (EC-GT) with breast cancer on day 18, cycle 2 from venous thrombo-embolism (VTE); one (EC-T) died from VTE 41 days after day 1, cycle 3; and one (EC-GT) from ischaemic heart disease 28 days after day 1 of cycle 2.

Dose Intensity

Complete information for dose intensity calculations was available on 3137 of the 3141 eligible patients (99·9%). EC-GT patients received moderately lower course-delivered dose intensity (CDDI) than EC-T patients (median (IQR) 96% (88-99) vs 98% (93-100), p<0·0001). Additionally, fewer EC-GT patients received CDDI ≥85% (80% (1261/1568) vs 89% (1395/1569), for EC-T patients, p<0·0001).

DISCUSSION

The *tAnGo* trial showed no benefit in either DFS or OS from the addition of gemcitabine to standard paclitaxel-containing, epirubicin/cyclophosphamide-based adjuvant chemotherapy in early breast cancer whereas toxicity was increased with more grade 3 myelosuppression, fatigue, and infection. We have the benefit of data from the tenth annual follow-up on 2121 patients (95% of the 2227 known to be alive) and therefore the results for all stratified risk groups are robust and are not unduly biased by length of follow-up[16]. The *tAnGo* trial was an all-comers trial carried out before the standard use of adjuvant trastuzumab for HER2 positive disease. At the start of the trial, adjuvant chemotherapy in the UK included paclitaxel for high-risk disease in very few centres. With the intention of ensuring that the results of the trial would be relevant in the future, we included paclitaxel in the standard arm, and at the start of the trial recruited only ER-negative and ER weakly positive patients, representing the highest risk population. In the second part of the trial the entry criteria were expanded to include moderate risk patients, because of emerging evidence at that point for more routine use of adjuvant taxanes[5,6]. The *tAnGo* trial was one of the last all-comers trials of its type in the UK and since then breast cancer type specific trials have been more frequent. The advantages of the permissive entry criteria used included rapid patient recruitment.

It is difficult to explain why the overall results were negative for adjuvant gemcitabine when the drug had been so promising in the metastatic setting[17], particularly given the ongoing positive results in metastatic TNBC[18]. Gemcitabine has recently been included in an international trial in metastatic TNBC with carboplatin and *nab*-paclitaxel[19,]. The first results of the Phase 2 feasibility study were presented at the San Antonio Breast Cancer Symposium in December 2016[20], and showed no benefit from the addition of gemcitabine. In view of this the trial (tnAcity study) will not proceed to a randomised phase III study. However there have been positive results in other solid tumours most notably pancreatic cancer[21]. Perhaps the addition of a fourth drug to three effective drugs is simply not going to improve DFS and OS in early breast cancer. The companion neoadjuvant trial (Neo-*tAnGo*) also showed no increase in pathological complete response (pCR) rate with the addition of gemcitabine and no improvement in DFS and OS[22]. In addition, neither the neoadjuvant NSABP-B40[22,23] trial examining both capecitabine and gemcitabine added to paclitaxel, nor the adjuvant NSABP-B38[8] using AC-TG as one of the experimental arms, showed any improvement in pCR or DFS and OS.

Since gemcitabine, an anti-metabolite, is in the same class of drugs as capecitabine, recent data on that drug is of interest. The adjuvant TACT 2 trial demonstrated that capecitabine has some advantages over standard CMF following anthracycline-based treatment [submitted, February 2017], because of lower toxicity and better quality of life with no apparent loss of efficacy. However, when capecitabine was added to docetaxel, doxorubicin and cyclophosphamide in the FINNXX trial[23], there was no improvement in DFS and when capecitabine was substituted for cyclophosphamide in the GEICAM/2003-10 Study there was an increase in DFS

events[24]. Nevertheless, there has been a recent renewal of interest with the use of capecitabine after neoadjuvant chemotherapy in patients who had not achieved a pCR in the CREATE-X study[25]. The benefits of this adjuvant treatment, were significant and most marked in the TNBC group (296 patients: HR 0·58 [95% CI 0·39-0·87]). However, it is unlikely that gemcitabine could be used in this setting because of the significantly higher toxicity particularly myelosuppression.

Are there potential subgroups in *tAnGo* in which increased benefit from adjuvant gemcitabine could be further explored? Two groups identified are the ER-negative/ grade3, HER2 positive or negative subsets (Figure 3c and p.8 Appendix)), which also showed a possible benefit for pCR in Neo-*tAnGo*[22]. Recent preclinical research has reported compelling results of relevance to gemcitabine use in breast cancer[26], showing that mutant p53 (mtp53) harbouring cells are highly sensitive to the cell killing effects of gemcitabine via inhibition of deoxycytidine kinase (dCK). In addition, dCK and/or p53 knockdown of these cells, abrogating the gain-of-function, conferred relative resistance to gemcitabine but not to cisplatin or doxorubicin. mtp53 status has been shown to be related to poor prognosis in breast cancer patients[27] and was recently studied in GEPAR SIXTO[28]. mtp53 was present in 297/450 (66%) patients, more frequently in TNBC (184/246 [74·8%]) compared to HER2-positive cancers (113/204 [55·4%] p<0·0001). As part of the *tAnGo* and Neo-*tAnGo* studies we have collected 80% of FFPE tumour samples for translational research and plan to explore this preclinical data further.

So what of the limitations of the *tAnGo* trial? Although a negative study, this is not itself a limitation and the study was carried out adhering to all the international

guidelines and governance for phase 3 randomised trials. The major limitation seen from the perspective of 2017 was the inclusion of all prognostic and biomarker subgroups in the same trial, which would not happen in present day trials. On the other hand this can be seen as a strength, because all subgroups were tested for the new treatment, and recruitment was more rapid since more patients were eligible. Such permissive entry criteria have served us well in the UK, and resulted in good and rapid recruitment to this and similar contemporaneous trials. The most important strength now is the minimum of 10 years follow-up and therefore the robustness of the (albeit negative) results.

In summary, the *tAnGo*, Neo-*tAnGo*, NSABP-B38 and NSABP-B40 trials all demonstrate a lack of activity when gemcitabine is added to three potent neo/adjuvant breast cancer chemotherapy drugs. *tAnGo* was a large, rapidly recruiting trial with sufficient follow up to allow confidence in this result. Parallel translational science for *tAnGo* is ongoing, including tumour genomic analysis, pharmacogenetics[29,30] and inherited predisposition analyses[31]. Clinical trials datasets, painstakingly collected and analysed, clearly need to be published fully including all negative studies. The publication of a 'negative' trial is as important for patients and the clinical research community as the positive trial results which lead to licensing approvals or change of practice that are generally perceived as more valuable. The rejection of gemcitabine from standard adjuvant breast cancer treatment for lack of benefit can be seen as a cost-effective result in terms of both financial and patient toxicity costs.

CONCLUSION

Gemcitabine in combination with paclitaxel after epirubicin and cyclophosphamide is not indicated in adjuvant breast cancer treatment with current biological characterisation. However, it seems likely that further improvements in the outcome of treatment for women with early breast cancer will depend on the development of targeted therapies, whose selective application is predicated on the biological heterogeneity of this disease.

RESEARCH IN CONTEXT

Evidence before this study

Gemcitabine had been used in metastatic breast cancer with significant benefit. The *tAnGo* trial which started in 2001, tested the addition of gemcitabine to standard anthracycline and taxane-based chemotherapy in the adjuvant treatment of early breast cancer. NSABP-B38 was the only other adjuvant breast cancer trial which added gemcitabine to standard chemotherapy. Two neoadjuvant breast cancer studies were undertaken: *NeotAnGo* was the companion study to *tAnGo*, which in a 2x2 factorial design tested both the addition of gemcitabine and taxane-first sequencing; and NSABP-B40 which in a 2x3 factorial design tested the addition of either gemcitabine or capecitabine, and also bevacizumab.

Added Value of this study

Early results from the tAnGo trial presented in 2008 showed no benefit in terms of DFS and OS and in this manuscript we report trial outcomes with a median follow-up of ten years. We demonstrate no benefit from the addition of gemcitabine to standard adjuvant chemotherapy in any prognostic sub-group. Recent pre-clinical research

suggests that gain-of-function mutations in TP53 may confer sensitivity to gemcitabine.

Implications of all the available evidence

Since the start of this trial the benefit of the addition of taxanes has been confirmed by the Early Breast Cancer Trialists' Collaborative Group overview. However, all neo/adjuvant clinical trials (*tAnGo*, *Neo-tAnGo*, NSABP-B38 and NSABP-B40) in early breast cancer show no advantage for the addition of gemcitabine to standard anthracycline and taxane-based chemotherapy. No sub-group has been identified showing gemcitabine benefit. Pre-clinical data suggesting gemcitabine sensitivity with TP53 gain-of-function mutations will be explored in the tAnGo translational tumour bank resource.

Contributors

CP was responsible for the grant writing, conception, design, trial co-ordination, data analysis and interpretation; as well as result interpretation, patient recruitment, and Chair of the Trial Steering Committee.

AMW was responsible for the grant writing, conception, design, trial co-ordination, data acquisition and interpretation; as well as result interpretation, manuscript drafting, patient recruitment, and sitting on the Trial Steering Committee.

HE was responsible for the grant writing, conception, design, data analysis and interpretation; as well as result interpretation, manuscript drafting, patient recruitment, and sitting on the Trial Steering Committee.

CC was responsible for the grant writing, conception, data acquisition and interpretation; as well as result interpretation, patient recruitment, and sitting on the Trial Steering Committee.

DC was responsible for the conception, design, data and result interpretation; as well as manuscript drafting, patient recruitment, and sitting on the Trial Steering Committee.

DD was responsible for the, design, trial co-ordination, data and result interpretation; as well as manuscript drafting, patient recruitment, and sitting on the Trial Steering Committee.

DWR was responsible trial co-ordination, data acquisition, analysis and interpretation; as well as result interpretation, manuscript drafting and patient recruitment.

JD was responsible for the grant writing, conception, design, result interpretation, manuscript drafting, and sitting on the Trial Steering Committee.

PC was responsible for the conception, design, data acquisition, result interpretation, patient recruitment, and sitting on the Trial Steering Committee.

LH was responsible for design, data analysis and interpretation, result interpretation, manuscript drafting, and sitting on the Trial Steering Committee.

JAC was responsible for the grant writing, conception, design and sitting on the Trial Steering Committee.

RC was responsible for design, manuscript drafting, patient recruitment and sitting on the Trial Steering Committee.

HH was responsible for the trial co-ordination, data acquisition and sitting on the Trial Steering Committee.

RL was responsible for design, patient recruitment and sitting on the Trial Steering Committee.

JPC was responsible for trial co-ordination, manuscript drafting and patient recruitment.

SB was responsible for trial co-ordination, data acquisition and manuscript drafting.

JA was responsible for the grant writing and patient recruitment.

AKW and JY were responsible for the trial co-ordination and data acquisition.

DMR and JK were responsible for the data acquisition and patient recruitment.

MM was responsible for the trial co-ordination.

EP was responsible for data acquisition.

AG, AB, GW, KM, RA, SO and TH were responsible for patient recruitment.

All authors revised the manuscript, approved the final manuscript, and agreed on all aspects of the work.

Declaration of interests

AMW reports personal fees from Roche, Pfizer, and AstraZeneca, as well as non-financial support and travel support from Amgen, and travel support from Celgene; all outside the submitted work.

CP reports grants and non-financial support from both Eli Lilly and Bristol Myers Squibb, and grants from Pfizer, during the conduct of the study; CP also reports grants, personal fees and non-financial support from Eli Lilly, Pfizer and Bristol Myers Squibb, outside the submitted work.

DC reports money to his institution for time spent on an IDMC for a Lilly sponsored trial from Lilly, outside the submitted work.

DD has taken part in teaching, educational services and consultancy for which honoraria were paid by various pharmaceutical companies but not Eli Lilly.

HE reports unrestricted educational grants and free bevacizumab from Roche, and unrestricted educational grants from Sanofi-Aventis, all for the ARTemis Trial as well as Advisory Board honorarium from Pfizer. All outside the submitted work.

JAC reports honoraria and consulting fees received from Lilly Industries Ltd and Bristol-Myers Squibb Pharmaceuticals Ltd, at the time of planning this study.

JPC reports non-financial support from Bristol Myers Squibb, outside the submitted work.

KM reports personal fees from Roche Medical Meeting, and Novartis Advisory Board for Metastatic Breast Cancer, outside the submitted work.

RC reports research grants from Bayer, Amgen and Celgene, to his institution outside the submitted work.

SB reports grants from Bristol-Myers Squibb Pharmaceuticals Ltd, and Lilly Industries Ltd., who provided free drug and an educational grant for the conduct of this study to the sponsor (her employer). SB also reports grants from Pharmacia (now Pfizer UK) who provided an educational grant, for the conduct of this study to the Sponsor (her employer) during the conduct of the study. BMS, Lilly Industries and Pharmacia had no input into the design, conduct, or interpretation of the study results.

TH reports grants from Roche, during the conduct of the study.

AB, AG, AKW, CC, DMR, DWR, EP, GW, HH, JA, JD, JK, JY, LH, MM, PC, RA, RL, and SO have nothing to disclose.

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FIGURE Legends

Figure 1: Trial Profile

Figure 2: Disease-free survival and overall survival by treatment group

Figure 3: Disease-Free Survival by Treatment, split by prognostic factors

Table 1: Patient Characteristics

			EC-GT (n=1570)		EC-T (n=1571)	
			N	%	N	%
*	Randomising Country	England	1282	81	1283	81
		Scotland	189	12	185	12
		Wales	66	4	72	4
		Republic of Ireland	30	2	27	2
		Northern Ireland	3	1	4	1
*	Age	≤50 years old	862	55	867	55
		>50 years old	708	45	704	45
*	ER Status	Negative	692	44	686	44
		Weakly-positive	168	11	197	12
		Positive	710	45	688	44
	PgR Status	Negative	695	44	703	45
		Weakly-positive	181	12	165	11
		Positive	524	33	510	32
		Unknown	170	11	193	12
*	Nodal Status	Negative	364	23	362	23
		1-3 nodes positive	648	41	646	41
		≥4 nodes positive	558	36	563	36
*	Radiotherapy planned	Yes	1412	90	1411	90
		No	158	10	160	10
*	HER2 status	+++	135	9	152	10
		Other (0, 1+, 2+)	1015	64	990	63
		Unknown	420	27	429	27

ECOG performance status	0	1433	91	1464	93
	1	135	8	106	6
	2	2	1	1	1
Menopausal Status	Pre	728	46	701	45
	Peri	104	7	131	8
	Post	560	36	556	35
	Bilateral Oophorectomy	14	1	12	1
	Hysterectomy	87	5	106	7
	Unknown	77	5	65	4
Definitive Surgery	Mastectomy	874	56	875	56
	Breast Conserving Surgery	696	44	696	44
Days from Definitive Surgery to Entry	N	1570		1571	
	Median (IQR)	31 (24 – 40)		32 (25 – 41)	
	Range	6 – 76		-9 – 80	
Triple negatives	Yes	364	23	362	23
	No	1028	66	1031	66
	Unknown	178	11	178	11
ER/PGR negatives	Yes	561	36	562	36
	No	955	61	946	60
	Unknown	54	3	63	4

***** Stratification variables at randomisation

^ 2 patients were randomised prior to definitive surgery, after authorisation from the Chief Investigator

Table 2: Disease-Free Survival according to treatment, patient and tumour characteristics

Variable	No. of patients*	No. of Events	p-value	DFS rates % (95% CI)		
				2 year	5 year	10 year
Overall	3141	1087		88 (86-89)	75 (73-76)	65 (63-67)
Treatment group			0·63			
EC-GT	1570	538		88 (87-90)	75 (73-77)	65 (63-68)
EC-T	1571	549		87 (85-88)	74 (72-76)	65 (62-67)
Number of nodes involved			<0·0001			
0	726	147		93 (91-95)	86 (84-89)	79 (76-82)
1-3	1294	378		91 (89-92)	79 (76-81)	71 (68-73)
4+	1121	562		80 (77-82)	62 (59-65)	50 (47-53)
Oestrogen-receptor status			<0·0001			
Negative	1378	513		82 (79-83)	69 (66-71)	62 (60-65)
Weakly-positive	365	130		86 (82-89)	74 (70-79)	64 (59-69)
Positive	1398	444		94 (92-95)	80 (78-82)	68 (66-71)
Progesterone-receptor status			<0·0001			
Negative	1398	517		83 (81-85)	69 (66-71)	63 (60-65)
Weakly-positive	346	129		87 (83-90)	74 (69-78)	62 (57-67)
Positive	1034	312		94 (93-96)	83 (80-85)	70 (67-72)
Radiotherapy planned			<0·0001			
Yes	2823	1012		87 (85-88)	73 (72-75)	64 (62-66)

No	318	75		95 (92-97)	86 (82-89)	76 (71-80)
Tumour size			<0·0001			
≤2cm	1122	280		92 (90-93)	82 (80-85)	75 (72-77)
>2 and ≤5cm	1663	648		86 (84-88)	71 (69-73)	61 (58-63)
>5cm	266	133		77 (71-81)	61 (55-67)	49 (43-55)
Tumour Grade			<0·0001			
Well differentiated	49	10		100 (100-100)	94 (82-98)	79 (65-88)
Moderately differentiated	1141	355		92 (91-94)	80 (78-83)	69 (66-71)
Poorly differentiated	1948	722		84 (83-86)	71 (69-73)	63 (60-65)
Vascular/Lymphatic invasion			<0·0001			
Reported	1836	752		84 (82-85)	69 (67-71)	59 (57-61)
Unreported	1303	335		93 (91-94)	82 (80-84)	74 (72-76)
Surgery			<0·0001			
Mastectomy	1749	673		86 (84-87)	72 (69-74)	61 (59-64)
Breast Conserving Surgery	1392	414		90 (88-91)	78 (76-80)	70 (67-72)
ECOG performance status			0·004			
0	2897	983		88 (87-89)	75 (74-77)	66 (64-68)
1 or 2	244	104		84 (79-88)	67 (60-72)	57 (51-63)
HER-2 status			0·0026			
+++	287	119		82 (77-86)	66 (60-71)	58 (52-64)
Other	2005	679		88 (87-90)	76 (74-78)	66 (64-68)

Age				0·80			
	≤50 years old	1729	596		87 (85-88)	73 (71-75)	65 (63-67)
	>50 years old	1412	491		88 (86-90)	76 (74-78)	65 (63-68)
Menopausal status				0·86			
	Pre	1429	489		88 (86-89)	74 (71-76)	65 (63-68)
	Peri	235	80		89 (84-92)	76 (70-81)	66 (59-71)
	Post	1116	397		87 (85-89)	76 (73-78)	64 (61-67)
Triple negatives				0·01			
	Yes	726	266		81 (78-84)	69 (65-72)	63 (59-66)
	No	2059	695		91 (89-92)	77 (75-79)	66 (64-68)
ER/PGR negative				0·0008			
	Yes	1123	412		81 (79-84)	69 (66-71)	63 (60-66)
	No	1901	626		92 (90-93)	78 (77-80)	67 (65-69)

* Patients with missing data for a given variable were excluded from the analysis of that variable

Table 3: Maximum reported grades of Adverse Effects during treatment by 3132 patients

	EC-GT (n=1565)			EC-T (n=1567)		
	1/2	**3**	**4**	**1/2**	**3**	**4**
Neutropenia	397 (25%)	323 (21%)	204 (13%)	364 (23%)	212 (14%)	200 (13%)
Myalgia/arthralgia	1140 (73%)	200 (13%)	7 (<1%)	1147 (73%)	175 (11%)	11 (1%)
Fatigue	1254 (80%)	198 (13%)	9 (1%)	1287 (82%)	140 (9%)	12 (1%)
Infection	578 (37%)	194 (12%)	8 (1%)	601 (38%)	131 (8%)	10 (1%)
Vomiting	786 (50%)	134 (9%)	9 (1%)	736 (47%)	101 (6%)	7 (1%)
Nausea	1271 (81%)	132 (8%)	-	1255 (80%)	102 (7%)	-
Neuro-sensory	1133 (72%)	83 (5%)	2 (<1%)	1174 (75%)	66 (4%)	3 (<1%)
Fever	332 (21%)	69 (4%)	1 (<1%)	235 (15%)	46 (3%)	3 (<1%)
Diarrhoea	648 (41%)	43 (3%)	1 (<1%)	607 (39%)	29 (2%)	0
Constipation	1086 (69%)	41 (3%)	1 (<1%)	1099 (70%)	24 (2%)	0
Dyspnoea	485 (31%)	37 (2%)	3 (<1%)	423 (27%)	30 (2%)	3 (<1%)
Stomatitis	1119 (72%)	31 (2%)	0	1095 (70%)	25 (2%)	0
Anaemia	873 (56%)	27 (2%)	1 (<1%)	629 (40%)	11 (1%)	3 (<1%)
Skin	703 (45%)	25 (2%)	0	651 (42%)	20 (1%)	1 (<1%)
DVT	4 (<1%)	17 (1%)	3 (<1%)	2 (<1%)	9 (1%)	3 (<1%)
Thrombocytopenia	130 (8%)	14 (1%)	4 (<1%)	75 (5%)	7 (<1%)	2 (<1%)
Cough	570 (36%)	10 (1%)	-	526 (34%)	4 (<1%)	-
Superficial Thrombophlebitis	367 (23%)	7 (<1%)	0	329 (21%)	1 (<1%)	1 (<1%)
Alopecia	1525 (97%)	-	-	1527 (97%)	-	-

No grade 5 adverse events were reported.

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Figure 1: Trial Profile

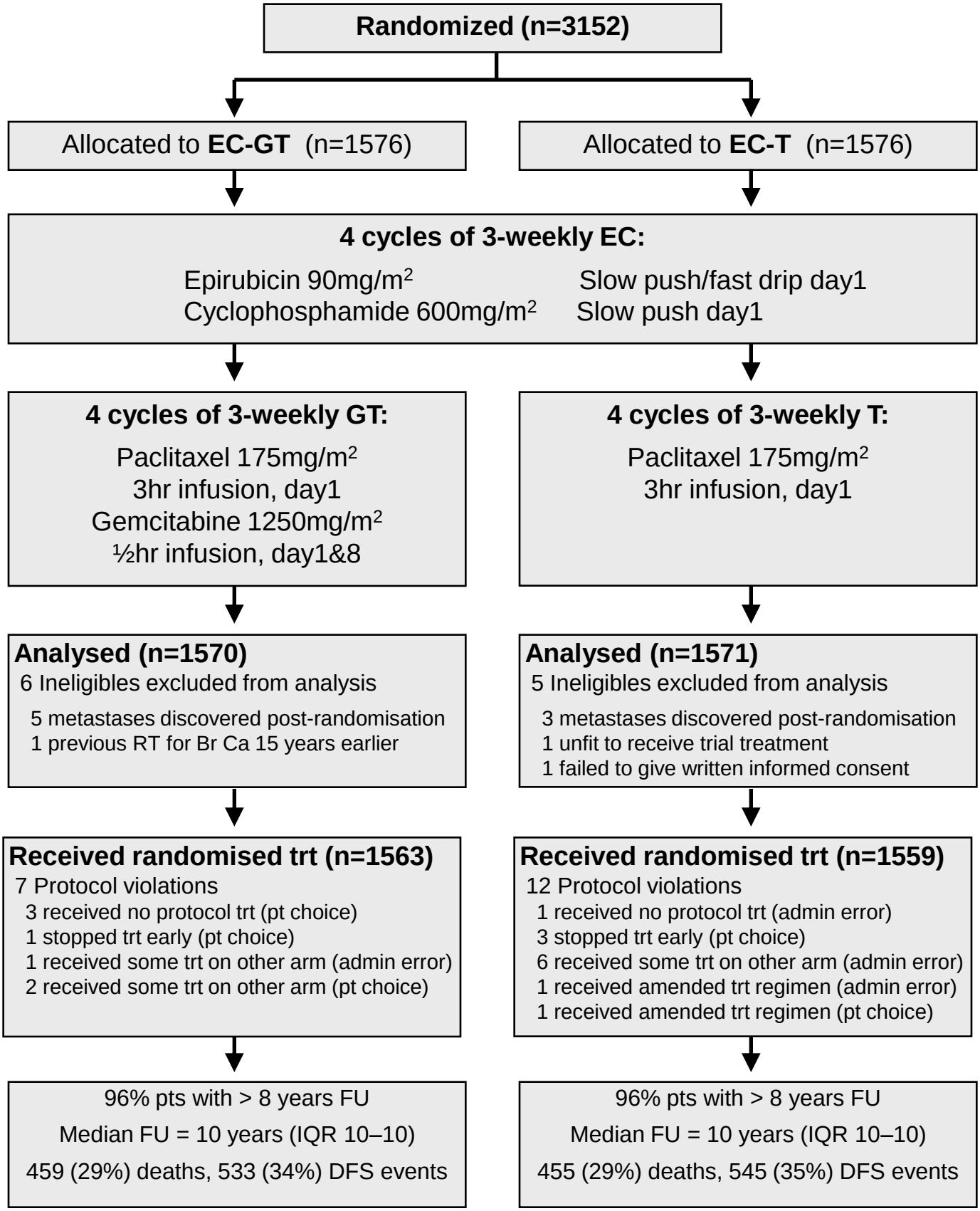
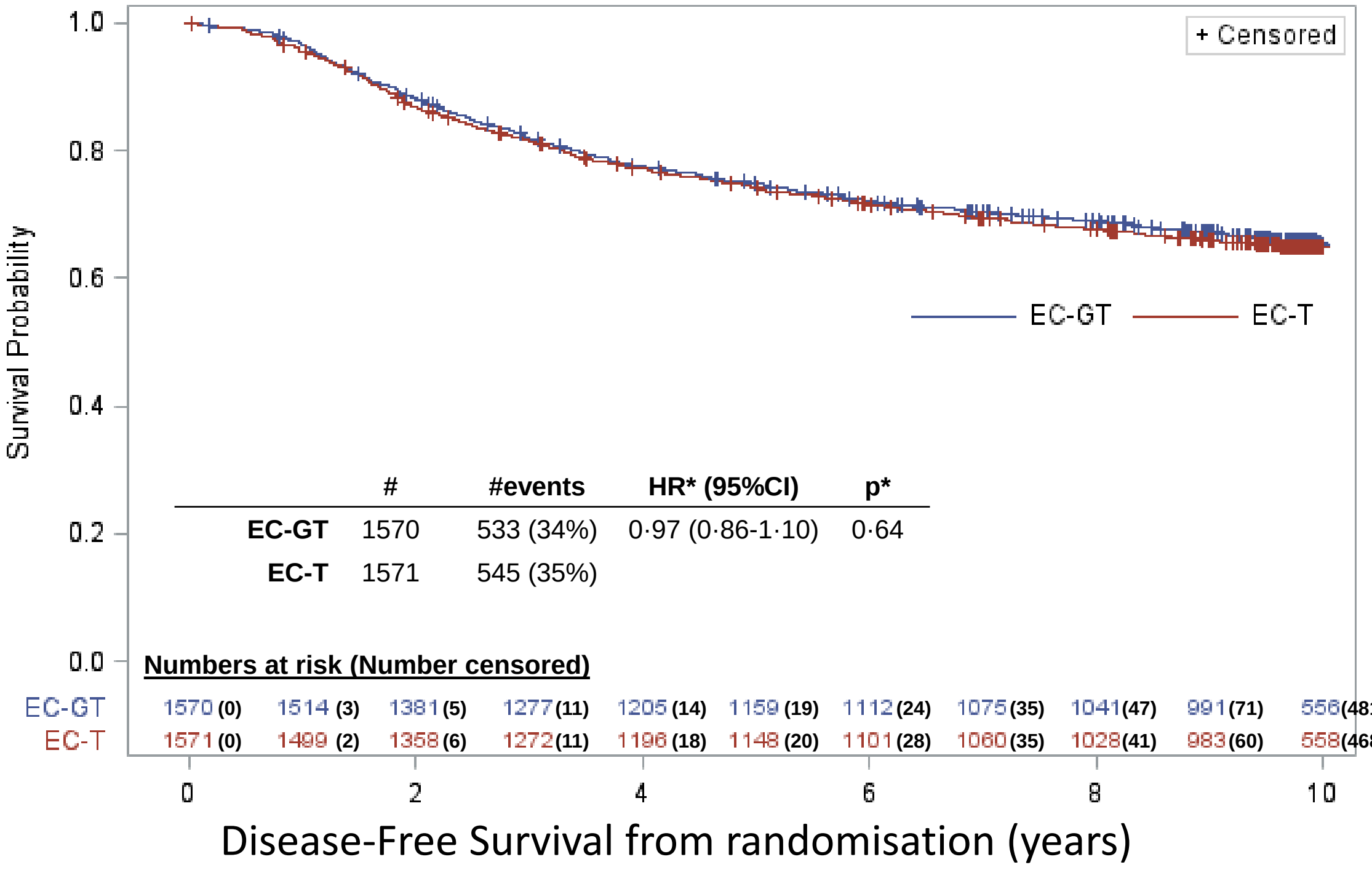


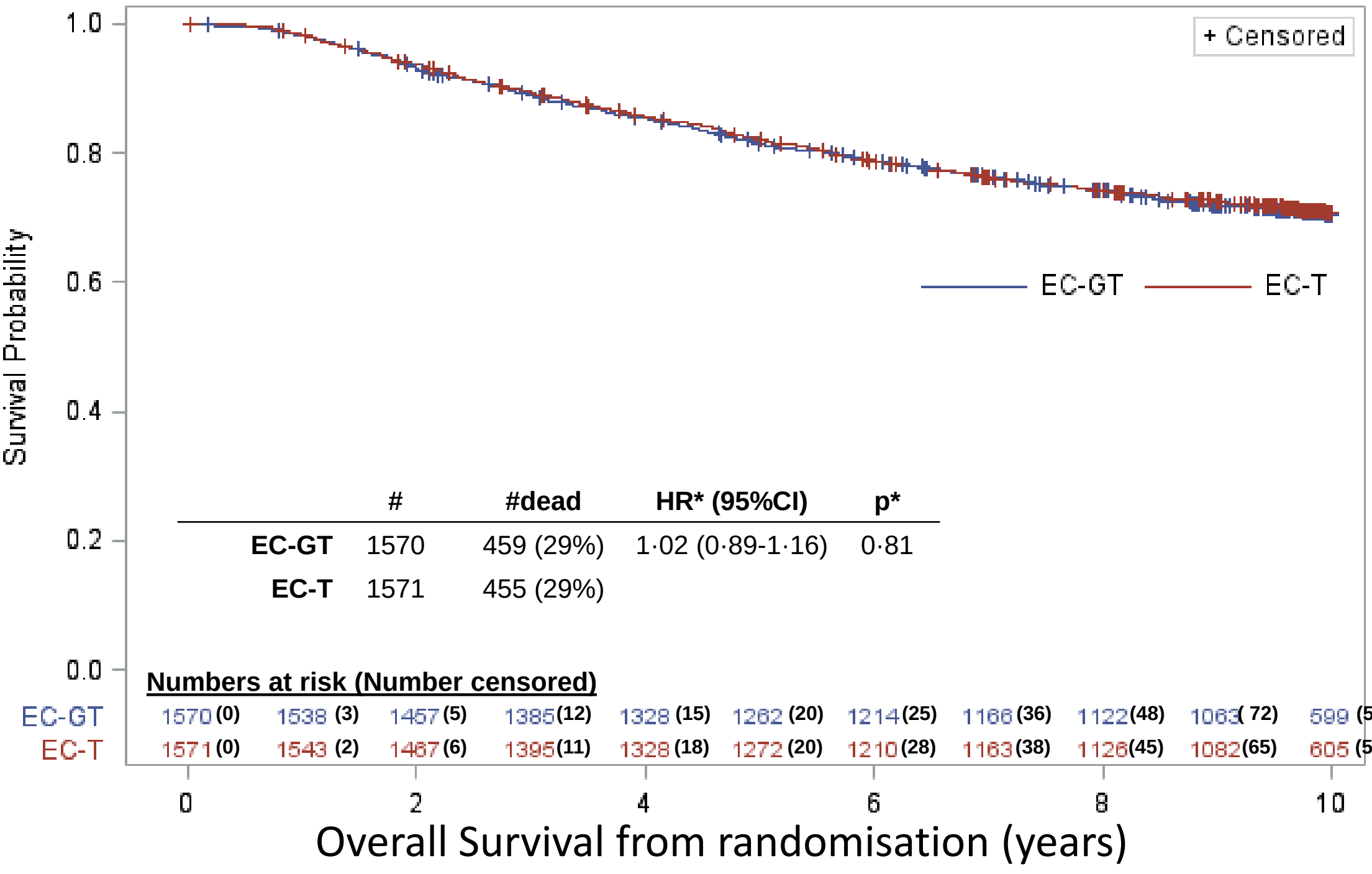
Figure 2 pdf

Figure 2: Disease-free survival and overall survival by treatment group

(a) Disease-Free Survival



(b) Overall Survival

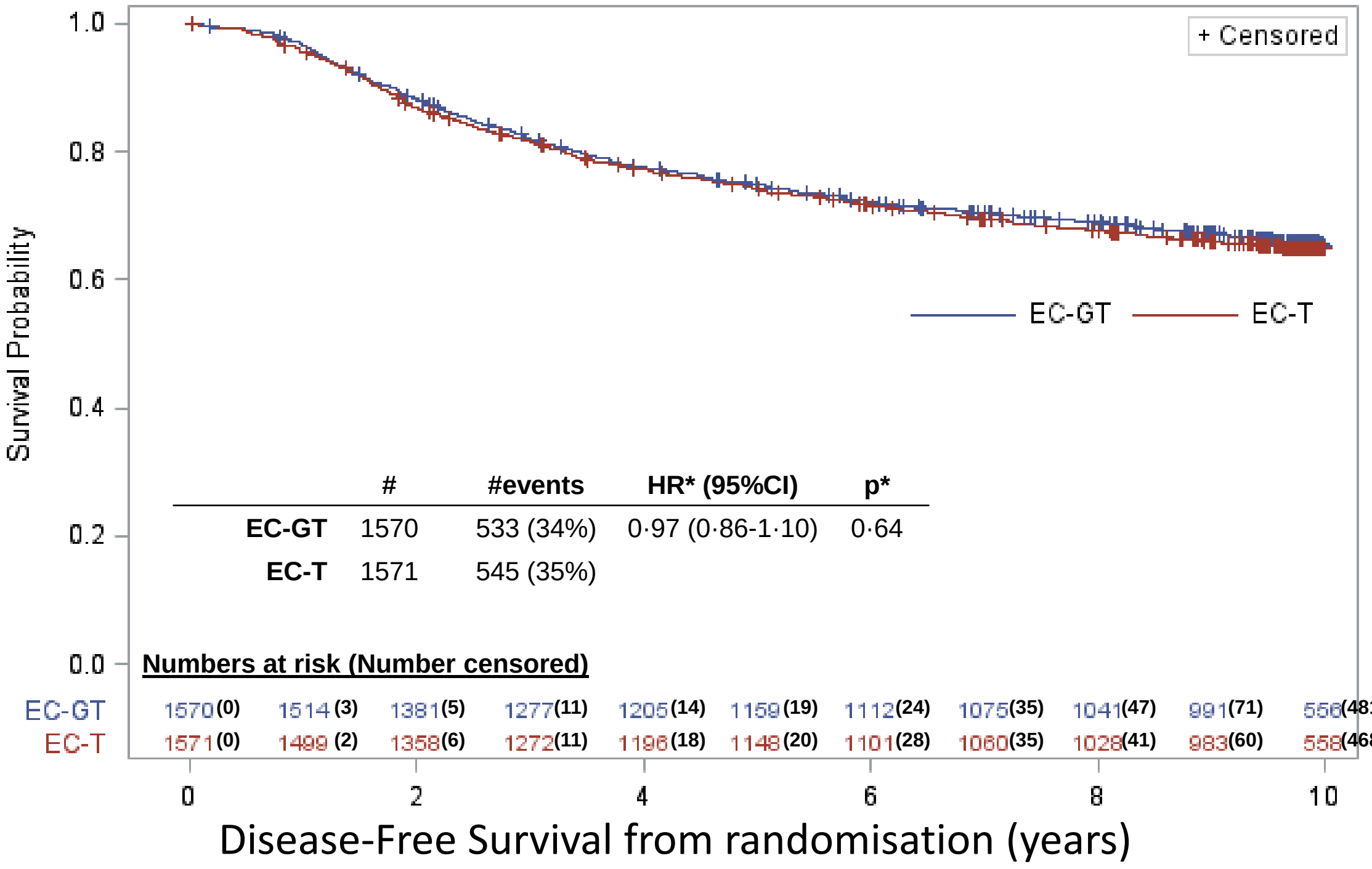


*** Adjusted for stratification variables**

Figure 2 pptx

Figure 2: Disease-free survival and overall survival by treatment group

(a) Disease-Free Survival



	#	#events	HR* (95%CI)	p*
EC-GT	1570	533 (34%)	0·97 (0·86-1·10)	0·64
EC-T	1571	545 (35%)		

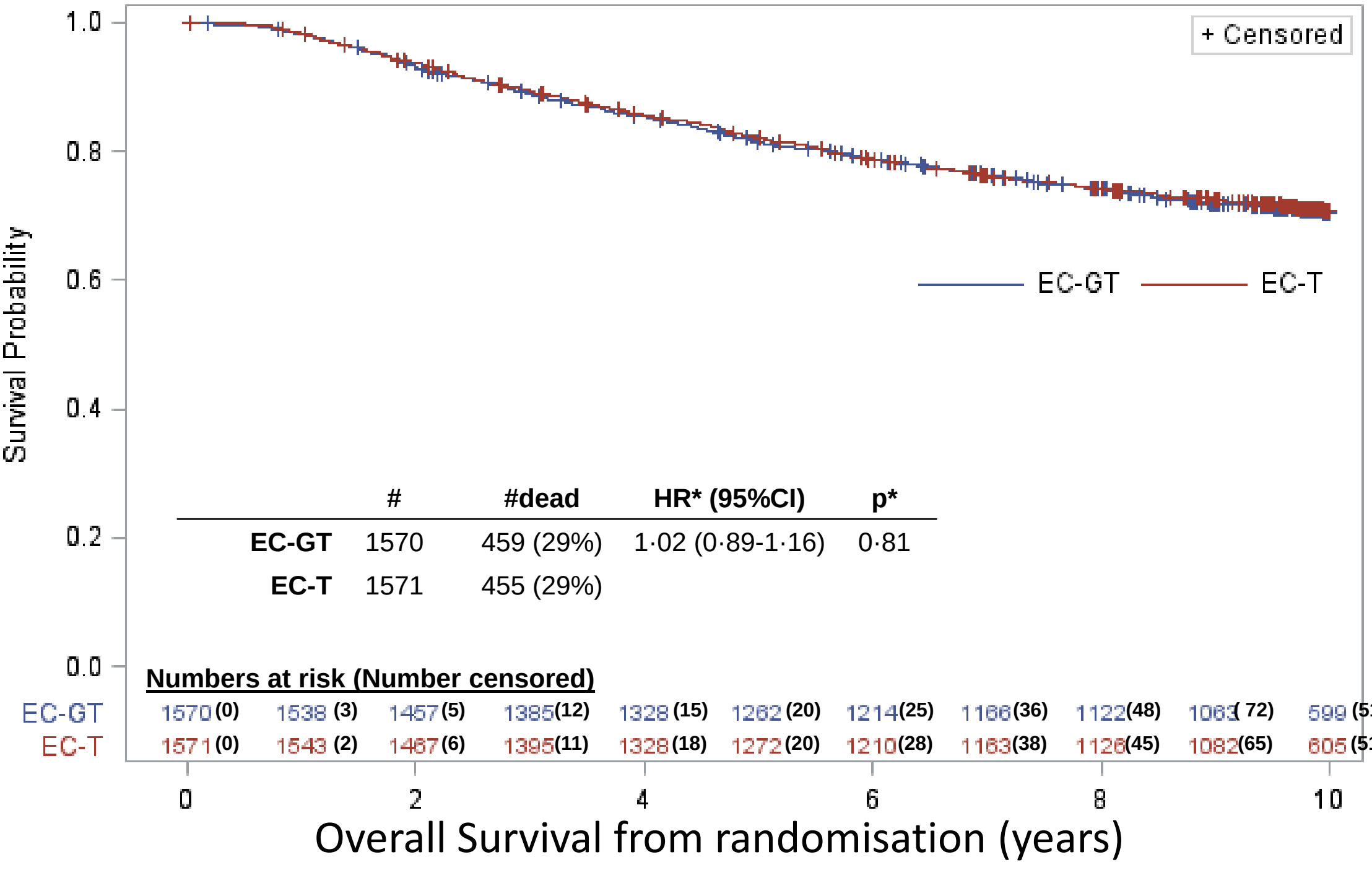
Numbers at risk (Number censored)

EC-GT	1570 (0)	1514 (3)	1381 (5)	1277 (11)	1205 (14)	1159 (19)	1112 (24)	1075 (35)	1041 (47)	991 (71)	556 (481)
EC-T	1571 (0)	1499 (2)	1358 (6)	1272 (11)	1196 (18)	1148 (20)	1101 (28)	1060 (35)	1028 (41)	983 (60)	558 (468)

0 2 4 6 8 10

Disease-Free Survival from randomisation (years)

(b) Overall Survival



	#	#dead	HR* (95%CI)	p*
EC-GT	1570	459 (29%)	1·02 (0·89-1·16)	0·81
EC-T	1571	455 (29%)		

Numbers at risk (Number censored)

EC-GT	1570 (0)	1538 (3)	1457 (5)	1385 (12)	1328 (15)	1262 (20)	1214 (25)	1166 (36)	1122 (48)	1063 (72)	599 (515)
EC-T	1571 (0)	1543 (2)	1467 (6)	1395 (11)	1328 (18)	1272 (20)	1210 (28)	1163 (38)	1126 (45)	1082 (65)	605 (517)

0 2 4 6 8 10

Overall Survival from randomisation (years)

*** Adjusted for stratification variables**

Figure 3a

Figure 3a: Disease-Free Survival by Treatment, split by prognostic factors (1)

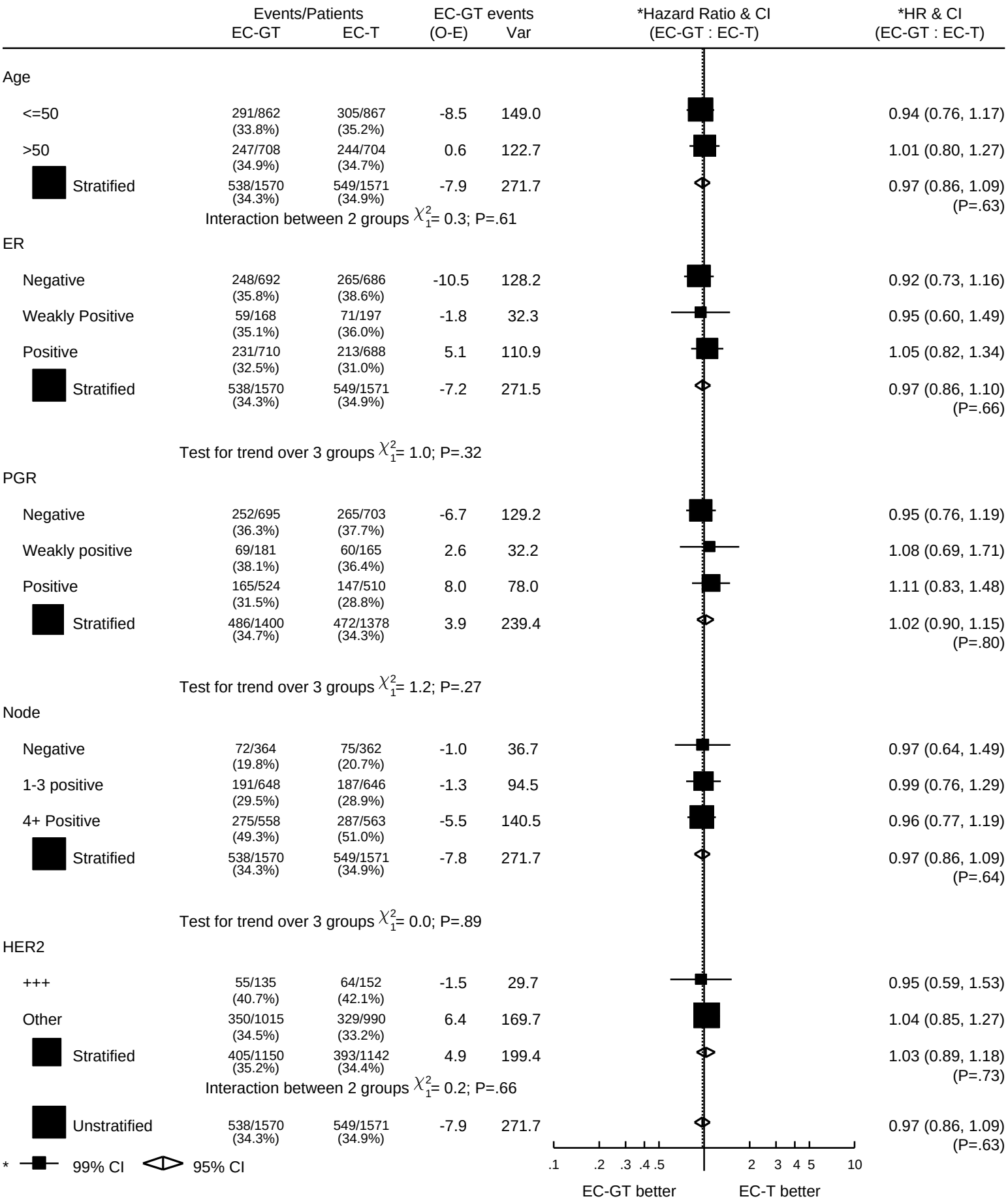


Figure 3b

Figure 3b: Disease-Free Survival by Treatment, split by prognostic factors (2)

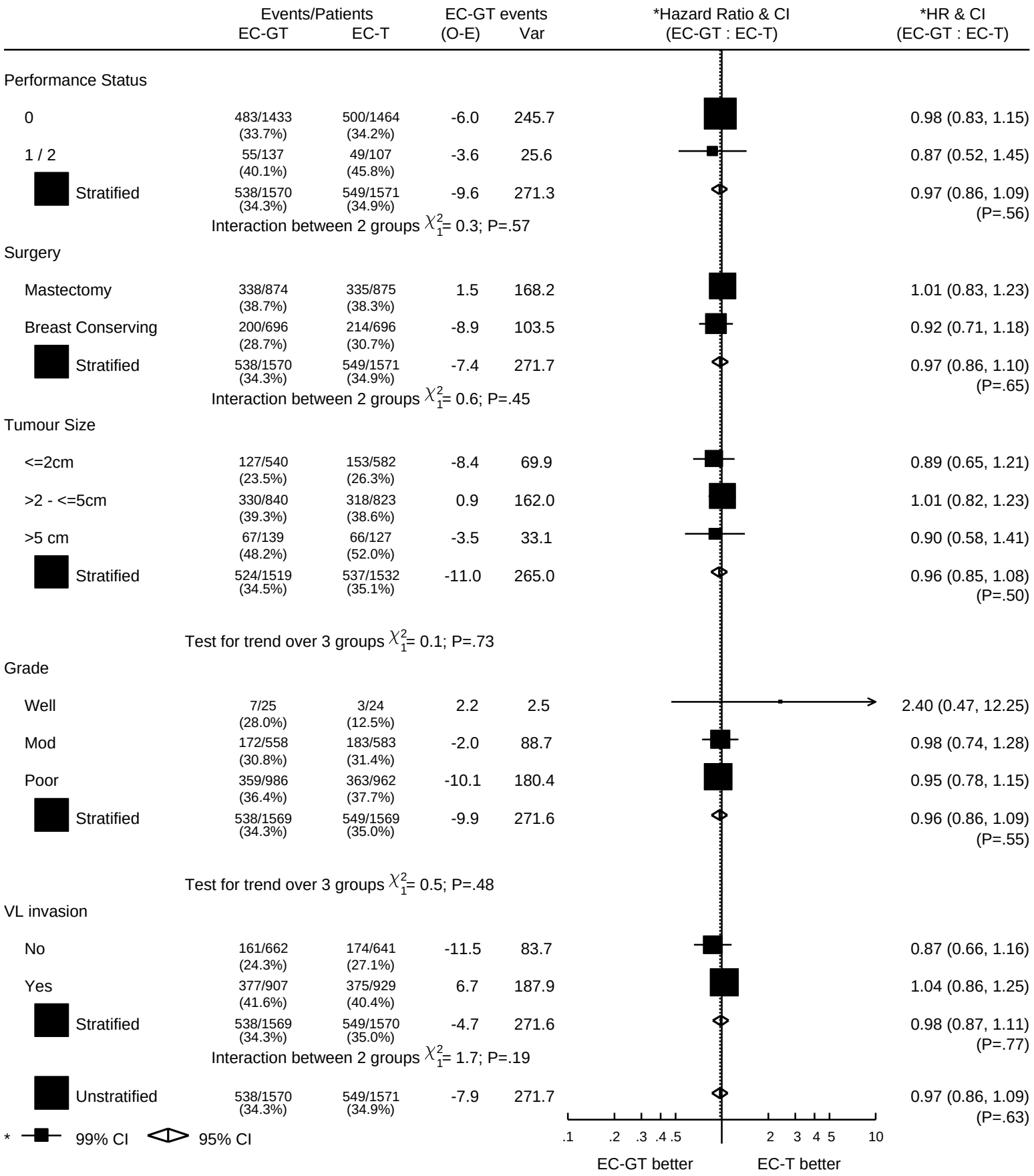
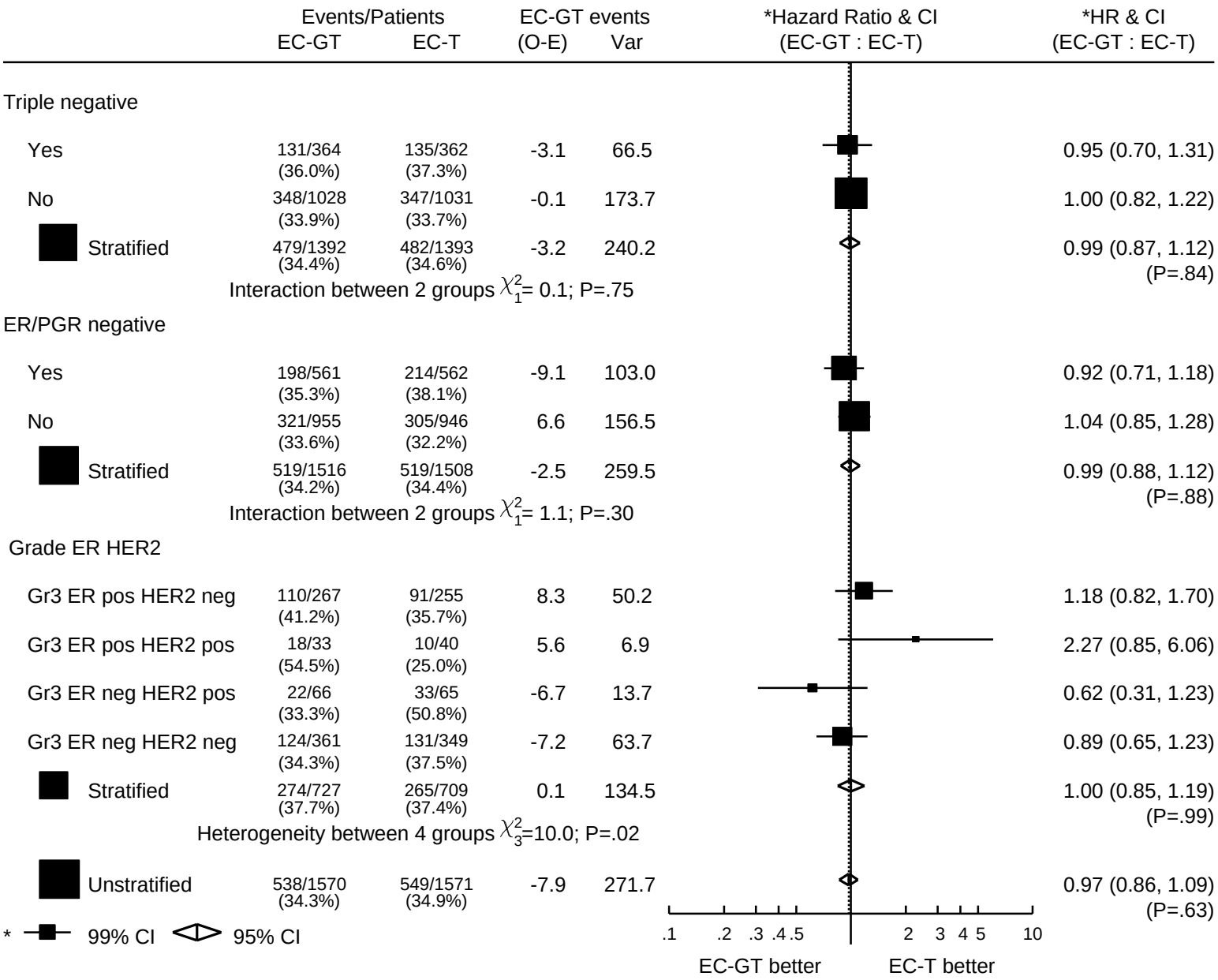


Figure 3c

Figure 3c: Disease-Free Survival by Treatment, split by prognostic factors (3)



Web Appendix

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